REMARKS

Reconsideration of this application is requested. Claims 13, 14, 16-23 and 25-28 are in the case.

I. THE INTERVIEW

At the outset, the undersigned wishes to thank the Examiner (Mr. Owens) for kindly agreeing to conducting a personal interview in this application. The interview was held on September 6, 2002, and the courtesies extended by the Examiner were most appreciated. The substance of the interview will be clear from the comments presented in the Interview Summary Record as well as the Discussion presented below.

II. THE ANTICIPATION REJECTION

Claims 1-28 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Granger, EP 466 650. That rejection is respectfully traversed.

Claims 1-12 drawn to the pharmaceutical formulation have been canceled without prejudice. The anticipation rejection as applied to those claims has accordingly been rendered moot.

As discussed during the interview, independent method claims 13 and 20 have been amended so as to specify that the alkali metal bicarbonate is selected from sodium bicarbonate, potassium bicarbonate and mixtures thereof. Claims 15 and 24

have been canceled without prejudice. The remaining dependent claims have been amended so as to be consistent with claims 13 and 20 and also to improve their form. No new matter is entered.

The method as claimed in this application is not anticipated by Granger. As conceded on page 4 of the Action, Granger does not disclose the T_{max} and C_{max} values. Moreover, as demonstrated by the attached executed Declaration evidence (discussed during the interview), the T_{max} and C_{max} values are not inherently achieved in view of the Granger disclosure.

The invention as claimed in claim 13 is directed to a method for generating an average C_{max} of Diclofenac comprised between 400 and 2500 ng/ml in a human patient in need of such a treatment, which comprises administering to the patient a pharmaceutical formulation containing from 10 to 60 mg of Diclofenac in acid and/or salt form together with an alkali metal bicarbonate selected from sodium bicarbonate, potassium bicarbonate and mixtures thereof and customary excipients and adjuvants. The alkali metal bicarbonate is present in an amount of from 20 to 80 % by weight based on the weight of Diclofenac.

The method as claimed in claim 20 is for obtaining an average T_{max} of Diclofenac after 5-30 minutes following administration in a human patient in need of such a treatment. The method comprises administering to the patient a pharmaceutical formulation containing Diclofenac in acid and/or salt form together with an alkali metal bicarbonate selected from sodium bicarbonate, potassium bicarbonate and mixtures thereof and customary excipients and adjuvants. The alkali metal bicarbonate is present in an amount of from 20 to 80 % by weight based on the weight of Diclofenac.

Referring to Granger, that reference describes various non-steroidal anti-inflammatory agents (NSAIDs) which operate systemically through inhibition of the biosynthesis of prostaglandins, particularly PGE_2. Granger notes that NSAIDs of this type fall into various classes based broadly on structure. Csaky and Barnes describe such NSAIDs as including, amongst others, fenamic acid derivatives, indene derivative, and ibufenac derivatives. At line 10 on page 2, Granger describes the broad classification of fenamic acid derivatives. Granger notes that fenamic acid derivatives are broadly classified as o-anilino derivatives of benzoic, phenylacetic, and nicotinic acids, and are defined by Csaky and Barnes as including flufenemic acid, mefenamic acid, meclofenamic acid, clonixeril, clonixin, flunixin, and diclofenac, as well as pharmaceutically-acceptable salts thereof (page 2, lines 10-12).

At page 2, beginning at line 13, examples of indene derivatives are described, and at page 2, beginning line 19, examples of ibufenac derivatives are describes. At page 2, beginning at line 36, Granger refers to the use of a non-toxic prostaglandin-stimulating metal base or basic salt in the manufacture of a medicament in the treatment of inflammation and states, at page 2, line 48, that the metal can be aluminum, magnesium, sodium, potassium, or bismuth. Granger also states that the metal base or basic salt can be the hydroxide, sulfate, carbonate, bicarbonate, subcarbonate, or trisilicate (page 2, lines 48 and 49).

The list of possible NSAIDs which can be used according to Granger comprises at least 34 different drugs (see page 2, lines 10-22). With regard to the metal, this can be aluminum, magnesium, sodium, potassium, or bismuth, and the metal base or basic salt may be the hydroxide, sulphate, carbonate, bicarbonate, subcarbonate or trisilicate.

Aluminum hydroxide is the preferred material, as can be seen from the Abstract and from the working examples. In particular, it is noted that there is no disclosure in the working examples of the use of diclofenac in combination with an alkali metal bicarbonate and, in particular, with sodium and/or potassium bicarbonate.

Granger thus discloses formulations consisting of (1) a NSAID selectable from at least 34 different possibilities, (2) a metal selectable from at least five different possibilities and (3) a base or salt selectable from at least six different possibilities. This computes to over 1,000 different possible combinations of components.

Granger provides no disclosure whatsoever relating to dissolution profiles or hematic levels which can be obtained by administering an oral formulation containing one of the possible disclosed combinations. Granger does not address this issue. Granger, as conceded in the action, relates to conferring a cytoprotective effect or reducing gastrointestinal inflammation.

The attached Declaration evidence establishes the lack of any inherent disclosure in Granger so far as the presently claimed method is concerned[1]. As demonstrated beginning on page 3 of the Declaration, Figure 1 depicts the dissolution curves for matrix tablets containing potassium bicarbonate (FII), magnesium carbonate (FIII) and calcium carbonate (FIV), in comparison with control unbuffered matrix tablets FI. The differences in the dissolution properties are striking. The same can be said for the results presented in Figure 2 shown on page 4 of the Declaration. Figure 2 shows dissolution curves for the matrix tablets containing potassium bicarbonate (FII), magnesium hydroxide (FV) and aluminium hydroxide (FVI), in comparison with the

unbuffered matrix tablets (FI). Again, the differences in dissolution profile are striking, further evidencing not only surprising results, but also a lack of predictability and thus lack of inherency with respect to the various possible combinations falling within the range of disclosure.

During the interview, it was agreed, as reflected by the Interview Summary Record, that the evidence established while Granger encompasses bicarbonate, there is no recognition that the particular bicarbonate forms employed according to the present invention would give the unexpected results as demonstrated. In addition, in paragraph 7 of the declaration, it is concluded formulations according to the present invention provide a more rapid dissolution of diclofenac than the formulations disclosed by Granger and, thus, provides for better pharmacokinetic profiles.

In light of the above, and in light of the attached Declaration evidence, it is believed that withdrawal of the outstanding anticipation rejection is in order. Such action is respectfully requested.

Allowance of the application is awaited.

[1] The undersigned has been advised that while the amount of potassium bicarbonate in the tablet of the present invention (FII) falls within the claimed range (20-80wt%), this is not the case for the other tablets (FIII to FVI) although the equivalents of the buffering agent correspond to those of FII.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

Respectfully submitted,

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Reiner Declaration under 37 CFR §1.132
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 1-12, 15 and 24 are canceled without prejudice.

13 (Amended). A method for generating an average C_{max} of Diclofenac comprised between 400 and 2500 ng/ml in a human [patients] patient in need of such a treatment, which comprises administering to [those patients] said patient a pharmaceutical formulation containing from 10 to 60 mg of Diclofenac in acid and/or salt form together with [alkali metal bicarbonates or mixtures thereof] an alkali metal bicarbonate selected from the group consisting of sodium bicarbonate, potassium bicarbonate and mixtures thereof and customary excipients and adjuvants, wherein said alkali metal [bicarbonates are] bicarbonate is present in [amounts] an amount of from 20 to 80 % by weight based on the weight of Diclofenac.

14 (Amended). A method according to claim 13 wherein said alkali metal [bicarbonates are] bicarbonate is present in [amounts] an amount of from 40 to 80 % by weight based on the weight of Diclofenac.

16 (Amended). A method according to claim 14 wherein said average C_{max} of Diclofenac is comprised between 1700 and 2300 ng/ml and said pharmaceutical formulation contains about 50 mg of Diclofenac in a form selected from the group consisting of its potassium salt form [and/or] and its sodium salt form.

17 (Amended). A method according to claim 14 wherein said average C_{max} of Diclofenac is comprised between 800 and 900 ng/ml and said pharmaceutical formulation contains about 25 mg of Diclofenac in a form selected from the group consisting of its potassium salt form [and/or] and its sodium salt form.

18 (Amended). A method according to claim 14 wherein said average C_{max} of Diclofenac is comprised between 400 and 500 ng/ml and said pharmaceutical formulation contains about 12.5 mg of Diclofenac in a form selected from the group consisting of its potassium salt form [and/or] and its sodium salt form.

19 (Amended). A method according to claim 13 wherein said average C_{max} of Diclofenac is reached after 13÷27 minutes [since] following administration.

20 (Amended). A method for obtaining an average T_{max} of Diclofenac after 5-30 minutes [since] following administration in a human [patients] patient in need of such a treatment, which comprises

administering to [those patients] said patient a pharmaceutical formulation containing Diclofenac in acid and/or salt form together with [alkali metal bicarbonates or] an alkali metal bicarbonate selected from the group consisting of sodium bicarbonate, potassium bicarbonate and mixtures thereof and customary excipients and adjuvants, wherein said alkali metal [bicarbonates are] bicarbonate is present in [amounts] an amount of from 20 to 80 % by weight based on the weight of Diclofenac.

21 (Amended). A method according to claim 20 wherein said T_{max} of Diclofenac is reached after 13-27 minutes since administration.

22 (Amended). A method according to claim 20 wherein said pharmaceutical formulation contains from 10 to 60 mg of Diclofenac in acid and/or salt form.

23 (Amended). A method according to claim 22 wherein said alkali metal [bicarbonates are] bicarbonate is present in [amounts] an amount of from 40 to 80 % by weight based on the weight of Diclofenac.

25 (Amended). A method according to claim 20 wherein said formulation is a pharmaceutical formulation for oral use comprising at least an immediate release layer and at least a delayed release layer, said immediate release layer containing Diclofenac in acid and/or salt form together with [alkali metal bicarbonates or] an alkali metal bicarbonate selected from the group consisting of sodium bicarbonate, potassium bicarbonate and mixtures thereof and customary excipients and adjuvants, wherein said alkali metal [bicarbonates are] bicarbonate is present in [amounts] an amount of from 20 to 80 % by weight based on the weight of Diclofenac.

26 (Amended). A method according to claim 25 wherein said second delayed release layer also contains Diclofenac as the active principle.

27 (Amended). A method according to claim 25 wherein said alkali metal

[bicarbonates are] bicarbonate is present in [amounts] an amount of from 40 to 80 % by weight based on the weight of Diclofenac.

28 (Amended). A method according to claim 27 [characterized in that] wherein said Diclofenac is present in its potassium and/or sodium salt form [and said alkali metal bicarbonates are potassium and/or sodium bicarbonates.]